Remarks

Claims 1 and 11-14 were pending in the subject application. By this Amendment, claims 1 and 11-14 have been amended and claims 3-10 have been cancelled. The undersigned avers that no new matter is introduced by this amendment. Accordingly, claims 1 and 11-14 are currently before the Examiner for consideration. Entry and consideration of the amendments presented herein is respectfully requested.

Submitted herewith are revocation and new powers of attorney appointing the undersigned to prosecute the subject application.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 for the subject application. Also submitted herewith is a Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

The applicants have amended claim 1 to recite that the therapeutic formulation comprises TIMP-1 antibodies, or Fab fragments thereof. In addition, claims 11-14 have been amended to lend greater clarity to the claimed subject matter. Support for these amendments can be found, for example, at page 3, lines 21-25, of the specification as originally filed.

The applicants gratefully acknowledge the Examiner's withdrawal of the previous rejections under 35 U.S.C. §112, second paragraph.

Claims 1 and 11-14 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The applicants respectfully traverse and submit that the claims are fully enabled by the subject specification. The applicants submitted several U.S. patents with the previous response, including patents demonstrating the use of antibodies for therapeutic treatment. The Office Action points out that none of the patents submitted by applicants used anti-TIMP-1 antibodies or prevented surgical adhesions and concludes "it is unclear how administering anti-TIMP-1 *in vivo* would prevent surgical adhesions". As indicated at page 5, lines 22-28, of the specification, the experimental data disclosed in the application suggests that adhesions exist in a molecular environment that prevents proteolytic degradation by matrix metalloproteinases (MMPs), and TIMP-1 may have a stimulatory effect on cell growth, including fibroblasts which migrate into the site of

injury at the initial stage of adhesion formation. Based on the correlation between TIMP-1 and the occurrence of surgical adhesions established by the experimental data, the applicants have developed a method for prevention or remediation of surgical adhesions by administering a therapeutic formulation containing anti-TIMP-1 antibodies to a patient. The teaching within the specification concerning the manner of making and using the subject invention must be taken as true unless the Patent Office can cite specific reasons to doubt the objective truth of the statements contained therein. *In re Marzocchi* 169 USPQ 367 (CCPA 1971).

At page 4, the Office Action states that "methods of preventing surgical adhesions using anti-TIMP-1 antibodies are not known in the art and considered an essential element of the claimed invention. Therefore, the amount of guidance and direction required is high to enable a person of ordinary skill in the art to practice the present invention." The applicants respectfully disagree. Rather, it is well settled in patent law that the standard is whether undue experimentation would be required by one of ordinary skill in the art in order to practice the claimed invention, given the benefit of the subject application. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

At page 4, citing Ward *et al.* (1994), the Office Action indicates that the current state of the art in antibody therapeutics and the predictability of treatment efficacy is complicated by various factors, such as "irrelevant or competing epitopes", "reduced half-life of antibody fragments", and "immune response to the therapeutic antibodies". This is not determinative of the enablement of the claimed invention. The applicants respectfully submit that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. The Federal Circuit has made it clear that the showing for therapeutic utility that is sufficient to satisfy the patent laws is not to be confused or equated with the showing required by the Food & Drug Administration for drugs, medical devices, and procedures. *Scott v. Finney*, 32 USPQ2d 1115 (Fed. Cir. 1994) and Manual of Patent Examining Procedure 2164.05. Given the state of the art, as demonstrated by the scientific publications submitted herewith, one of ordinary skill in the art can readily determine appropriate dosages, routes of administration, *etc.*, without resort to undue experimentation. Thus, the applicants respectfully submit that the subject specification enables the claimed antibody-mediated treatment methods.

Although the applicants submit that the Patent Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, submitted herewith for the Examiner's consideration are several scientific papers published prior to the priority date of the subject application.

Submitted herewith are the following scientific publications that demonstrate the successful use of antibodies that interfere with the function of their target antigens *in vivo*: Rothlein R. *et al.*, "Treatment of Inflammation with Anti-ICAM-1", *Res. Immunol.*, 1993, 144(9):735-739; Wegner C. *et al.*, "Efficacy of Monoclonal Antibodies Against Adhesion Molecules in Animal Models of Asthma", *Agents Actions Suppl.*, 1993, 43:151-162; Zhang R. *et al.*, "Anti-ICAM-1 Antibody Reduces Ischemic Cell Damage After Transient Middle Cerebral Artery Occlusion in the Rat", *Neurology*, 1994, 44(9):1747-1751; Maguire H. *et al.*, "Neutralizing Anti-IL-10 Antibody Upregulates the Induction and Elicitation of Contact Hypersensitivity", *J. Interferon Cytokine Res.*, 1997, 17(12):763-768; Iimuro Y. *et al.*, "Antibodies to Tumor Necrosis Factor Alfa Attenuate hepatic Necrosis and Inflammation Caused by Chronic Exposure to Ethanol in the Rat", *Hepatology*, 1997, 26(6):1530-1537; Walter U. *et al.*, "Generation and Characterization of a Novel Adhesion Function Blocking Monoclonal Antibody Recognizing Both Rat and Mouse E-Selectin", *Hybridoma*, 1997, 16(4):355-361; Petit A. *et al.*, "Neutralizing Antibodies Against Epidermal Growth Factor and ErbB-2/neu Receptor Tyrosine Kinases Down-Regulate Vascular Endothelial Growth Factor Production by Tumor Cells *In Vitro* and *In Vivo*", *Am. J. Pathol.*, 1997, 151(6):1523-1530; van Deventer S. and Comoglio L., "Monoclonal Antibody Therapy of Inflammatory Bowel Disease", *Pharm. World Sci.*, 1997, 19(2):55-59; Lorenz H. *et al.*, "*In Vivo* Blockade of TNF-α by Intravenous Infusion of a Chimeric Monoclonal TNF-α Antibody in Patients with Rheumatoid Arthritis", *J. Immunol.*, 1996, 156(4):1646-1653; Henricks P. and Nijkamp F., "Pharmacological Modulation of Cell Adhesion Molecules", *Eur. J. Pharmacol.*, 1998, 344(1):1-13; and Yamasaki Y. *et al.*, "New Therapeutic Possibility of Blocking Cytokine-Induced Neutrophil Chemoattractant on Transient Ischemic Brain Damage in Rats", *Brain Res.*, 1997, 759(1):103-111. As demonstrated by the foregoing scientific publications, function-blocking antibodies have been utilized to interfere with the activities of various adhesion molecules and cytokines.

As indicated in the Written Restriction requirement dated October 2, 2002, U.S. Patent No. 5,744,442 (Richards *et al.*) describes a polyclonal antibody to TIMP-1. Furthermore, submitted with the IDS accompanying this Amendment is the Forough *et al.* publication (Forough, R. *et al.*, "Generating Antibodies Against Secreted Proteins Using Vascular Smooth Muscle Cells Transduced with Replication-Defective Retrovirus", *BioTechniques* 20:694-701, 1996), which describes an anti-TIMP-1 antibody capable of inhibiting the activity of TIMP-1 *in vivo* (see lines 25-28 of the abstract and pages 699-701). In addition, various other means of inhibiting TIMP-1 have been utilized in the art, such as anti-sense RNA and targeted gene disruption, as demonstrated by the Khokha *et al.* publication and Alexander and Werb publication, respectively (Khokha R. *et al.*, "Antisense RNA—Induced Reduction in Murine TIMP Levels Confers Oncogenicity on Swiss 3T3 Cells", *Science, New Series*, 243(4893):947-950, 1989; Alexander, C. and Werb, Z., "Targeted Disruption of the Tissue Inhibitor of Metalloproteinases Gene Increases the Invasive Behavior of Primitive Mesenchymal Cells Derived from Embryonic Stem Cells *In Vitro*", *J. Cell Biology*, 118(3):727-739, 1992), which are submitted with the IDS accompanying this Amendment.

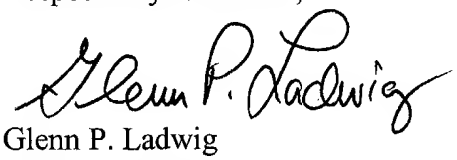
Accordingly, the applicants respectfully submit that, given the teaching of the specification and the state of the art in antibody production and antibody therapeutics, one of ordinary skill in the art could carry out the claimed methods without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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GPL/mv

Attachments: Petition and Fee for Extension of Time
Copy of Revocation and New Power of Attorney
Request for Continued Examination (RCE) under 37 C.F.R. §1.114
Information Disclosure Statement, including Form PTO/SB/08
Rothlein, R. *et al.*, *Res. Immunol.*, 1993, 144(9):735-739
Wegner, C. *et al.*, *Agents Actions Suppl.*, 1993, 43:151-162
Zhang, R. *et al.*, *Neurology*, 1994, 44(9):1747-1751
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Yamasaki, Y. *Brain Res.*, 1997, 759(1):103-111